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Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: *Comments of Lavipharm Laboratories on Citizen Petitions, Docket Nos. 2004P-0340, 2004P-0472, 2004P-0506 and 2004P-0540*

On behalf of Lavipharm Laboratories ("Lavipharm"), we are submitting these comments in response to the above-referenced Citizen Petitions. Notably, all of these petitions, except for one, has been filed by persons or an entity with a direct and obvious connection to Johnson & Johnson ("J&J"), the parent company of Alza Corporation ("Alza") and Janssen Phamaceutica Products, L.P. ("Janssen"), the two companies which manufacture and distribute, respectively, the Duragesic Fentanyl Transdermal System ("Duragesic FTS"). More specifically, one of the Citizen Petitions was filed by Alza (Docket No. 2004P-0506), while two of the other Citizen Petitions were filed by physicians who disclosed an affiliation with Alza and Janssen. *See* Dr. Shafer Citizen Petition (Docket No. 2004P-0340); Drs. Brookoff and Voth Citizen Petition (Docket No. 2004P-0472). The final petition, filed by an attorney with the law firm of London and Mead, does not indicate whether the petitioner has any relationship to J&J, Alza or Janssen.

All these Citizen Petitions were filed on the eve of January 23, 2005, the date on which J&J's pediatric exclusivity for the Duragesic FTS is set to expire. The timing of these petitions,

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combined with the connection the authors have to J&J, amounts to a concerted campaign by J&J to delay the approval of pending Abbreviated New Drug Applications ("ANDAs") and to stall the introduction of generic forms of Duragesic into the market. These petitions, however, do not present any reason for denying Lavipharm's ANDA.

Lavipharm has an interest in these petitions because it has submitted an ANDA for a generic fentanyl transdermal system, and each of these petitions suggests that additional requirements should be imposed upon all ANDA applicants, including Lavipharm, (*e.g.*, more stringent requirements for bioequivalence, new requirements for pharmaceutical equivalence, or implementation of a risk management system) before such applications are approved by the Food and Drug Administration ("FDA").

We have reviewed the December 10, 2004 and December 30, 2004 comments of Noven Pharmaceuticals, Inc. ("Noven") on two of the above-referenced Citizen Petitions (Docket Nos. 2004P-0472 and 2004P-0540), and the comments of Mylan Technologies, Inc. ("Mylan") with regard to the other Citizen Petitions (Docket Nos. 2004P-0340 and 2000P-0506). Since many of the points made in those comments support Lavipharm's position, we will not repeat the responses to the Citizen Petitions contained in those comments. We are submitting these comments in order to explain the unique nature of Lavipharm's fentanyl transdermal product, which provides an additional basis for rejecting many of the arguments in the petitions, as applied to Lavipharm, and to make several other points.

As discussed below, the Lavipharm Fentanyl Transdermal System ("Lavipharm FTS") is a solid state matrix system with a rate-controlling membrane. The combination of these two features in a single product renders the Lavipharm FTS distinct from both the Duragesic FTS and, to the best of our knowledge, other generic fentanyl transdermal systems. Based on this,

other information contained in these comments, and the comments submitted by Mylan and Noven, Lavipharm requests that FDA deny the above-referenced Citizen Petitions before January 23, 2005, the date on which pediatric exclusivity for the Duragesic FTS is set to expire. At a minimum, since these petitions were filed in a last-ditch effort to delay the introduction of generic fentanyl transdermal systems to the market and raise no colorable basis for denying applications to market generic versions of the Duragesic FTS, even if FDA is unable to issue a decision on the petitions by January 23, 2005, it should approve, on January 23, 2005, any pending, and otherwise approvable, ANDAs.

I. The Lavipharm Fentanyl Transdermal System

The Lavipharm FTS is a generic version of the Duragesic FTS, a transdermal fenatanyl patch designed to deliver fentanyl through the skin for the treatment of chronic pain over a period of three days. The Lavipharm FTS is available in the same four dosage forms as the Duragesic FTS and, like the Duragesic FTS, the Lavipharm FTS delivers the fentanyl over a period of three days.

The Lavipharm FTS contains the same five functional layers as the Duragesic FTS. From top to bottom, both the Lavipharm FTS and the Duragesic FTS contain: (1) an impermeable backing; (2) a drug reservoir; (3) a rate-controlling membrane; (4) a skin adhesive; and (5) a protective liner. The function of each of these five layers is as follows: the impermeable backing serves as a barrier to assure the drug is delivered only on the adhesive side of the product; the drug reservoir serves as the primary residence site for the drug during storage of the product; the rate-controlling membrane regulates the rate of fentanyl delivery; the skin adhesive attaches the patch to the skin of the patient; and the protective liner protects the adhesive during storage in the package.

Notwithstanding all of the similarities, there is one important difference between the two products: the design of the drug reservoir layer. In the Lavipharm FTS, the drug reservoir is solid and is composed of an adhesive matrix similar to the skin adhesive, while the drug reservoir in Duragesic FTS is liquid. The solid reservoir design of the Lavipharm FTS yields a patch that is less bulky than the Duragesic FTS and one that adheres more consistently than the Duragesic FTS, as has been demonstrated in clinical studies.

In sum, the Lavipharm FTS is, to the best of our knowledge, the only fentanyl transdermal system which combines a solid state matrix system with a rate-controlling membrane. As discussed below, the result of this technology is a product that is invulnerable to many of the attacks leveled by the Citizen Petitions referenced above.

II. The Contentions in Dr. Shafer's Citizen Petition (Docket No. 2004P-0340) Do Not Apply to Lavipharm FTS.

In his Citizen Petition (Docket No. 2004P-0340), Dr. Steven L. Shafer asks FDA to require an ANDA applicant for a generic transdermal fentanyl product to demonstrate bioequivalence to the Duragesic FTS "on both intact skin and on skin in which the stratum corneum has been stripped." Dr. Shafer Citizen Petition (Docket No. 2004P-0340) at 1. The concerns raised by Dr. Shafer do not apply to the Lavipharm FTS.

Dr. Shafer argues that "fentanyl will flow from a transdermal system into the systemic circulation far more rapidly across stripped skin than across skin with intact stratum corneum." *Id.* at 2. Dr. Shafer states that rapid fentanyl absorption through stripped skin is targeted at generic transdermal fentanyl systems that lack a rate-controlling membrane or similar mechanism to control the rate of fentanyl delivery. While certain generic transdermal fentanyl systems lack a rate-controlling membrane, the Lavipharm FTS does not. The Lavipharm FTS

contains a rate-controlling membrane, which controls the release and delivery rate of fentanyl. Therefore, at a minimum, Dr. Shafer's petition should be denied with respect to the Lavipharm FTS.

III. The Diversion, Abuse and Safety Issues Raised by the Citizen Petitions Are Not Grounds for Delaying Approval of the ANDAs and Do Not Apply to the Lavipharm FTS.

The Citizen Petition submitted by Alza (Docket No. 2004P-0506) and the Citizen Petition submitted by Drs. Brookoff and Voth (Docket No. 2004P-0472) argue that products using the solid state matrix delivery system are more susceptible to diversion and abuse and are less safe than the reservoir system used in the Duragesic FTS. The Citizen Petition submitted by London & Mead (Docket No. 2004P-0540) also asserts that solid state matrix products are less safe than the Duragesic FTS. Notably, Alza's criticism of solid state matrix delivery systems is undermined by its own actions which it discloses in its petition. Alza has introduced its own matrix delivery system product in Europe and is phasing out its reservoir system product in those markets to which it has introduced its matrix product. *See* Alza Citizen Petition (Docket No. 2004P-0506) at 3.

In their comments on these Citizen Petitions, and that of London & Mead, Mylan and Noven have responded thoroughly to the issues raised by the petitions. *See* Mylan Comments to Alza Citizen Petition (Docket No. 2004P-0506), December 10, 2004; Noven Comments to Drs. Brookoff and Voth Citizen Petition (Docket No. 2004P-0472), December 10, 2004; Noven Comments to London & Mead Citizen Petition (Docket No. 2004P-0540), December 30, 2004. Accordingly, we will not restate the arguments that are set forth in these earlier comments. We will instead explain why, because of its unique design, the Lavipharm FTS (a solid state matrix

product with a rate-controlling membrane), has advantages as compared to the Duragesic FTS and other solid state matrix products.

As previously stated, the Lavipharm FTS is a solid-state matrix system that also has a rate-controlling membrane. The Lavipharm FTS has been designed with a membrane equivalent in barrier properties to the membrane in the Duragesic FTS; these membranes impose an upper limit on the potential rate of fentanyl delivery. The membrane in the Lavipharm FTS provides the same advantages for patients as the membrane used in the Duragesic FTS and has some additional advantages as well. Unlike the membrane used in the Duragesic FTS, the membrane in the Lavipharm FTS does not serve a dual function of diffusion control and physical containment of the reservoir. A breach in the Duragesic FTS membrane leads to leakage of the liquid reservoir and can cause potentially dire health consequences. In its Citizen Petition, Alza even acknowledged that such leakage can occur. Alza Citizen Petition, Docket No. 2004P-0506 at 3 ("Matrix products do afford some advantages over reservoir products in terms of cosmetics adhesion, and in the elimination of possible get leakage."). By comparison, because the reservoir in the Lavipharm FTS is solid, a breach in the membrane does not allow leakage, and any minor breach does not affect the diffusion control function of the membrane.

The dangers associated with leakage in the Duragesic patch are significant, as evidenced by the recent recall notices issued by Janssen on February 17, 2004 and April 5, 2004, for certain lot numbers of the Duragesic FTS. Such leakage can result in a fatal overdose of fentanyl. As Janssen stated in its February 17, 2004 recall notice: "Exposure to the Duragesic hydrogel contents could result in an increased absorption of the opiod component, fentanyl, leading to increased drug effect, including nausea, sedation, drowsiness, or potentially life threatening

complications." Janssen Recall Notice for Duragesic, February 17, 2004. Based on the design of the Lavipharm FTS, the same type of leakage would not occur in the Lavipharm FTS.

Moreover, to the extent the Citizen Petitions argue that solid matrix systems generally are more susceptible to diversion, the rate-controlling membrane that is present in the Lavipharm FTS provides additional protection against such potential abuse. If a person were to cut up the Lavipharm FTS and apply it to his or her mucosa to be absorbed, each individual piece would contain the intact membrane, which would limit the release of fentanyl from the patch through the membrane and limit the absorption rate, thereby minimizing the potential for abuse.

IV. FDA May Not Classify Different Transdermal Fentanyl Delivery Systems as Different Dosage Forms.

In its Citizen Petition, Alza asks FDA to "classify matrix and reservoir fentanyl transdermal systems, as well as products with and without rate-controlling membranes, as different dosage forms that are not pharmaceutical equivalents." Alza Citizen Petition (Docket No. 2004P-0506) at 1.[1] Alza argues that because (1) the Duragesic FTS has a different delivery mechanism from certain of the generic fentanyl transdermal systems; and (2) according to Alza, certain of these delivery systems are more susceptible to abuse and rapid fentanyl delivery than others (as explained above, this argument does not apply to the Lavipharm FTS), FDA should classify these different technologies as different dosage forms. *Id.* at 2, 7-9. Mylan's comments to Alza's Citizen Petition effectively rebut Alza's argument that the different fentanyl delivery systems should be classified by FDA as different dosage forms. *See* Mylan Comments to Alza Citizen Petition (Docket No. 2004P-0506), December 10, 2004.

[1] London & Mead makes a similar argument in its Citizen Petition (Docket No. 2004P-0540). Although London & Mead does not argue for FDA to classify different delivery mechanisms as different delivery forms, it does argue that generic fentanyl transdermal systems should be required to have the same delivery mechanism as the Duragesic FTS. L&M's argument is refuted by Noven. *See* Noven Comments on London & Mead Citizen Petition (Docket No. 2004P-0540), December 30, 2004.

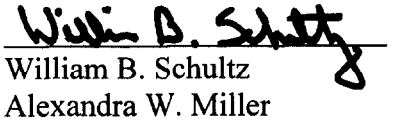
We would like to emphasize an important point made by Mylan: a review of FDA precedent reveals that "FDA has never treated generic systems as different dosage forms despite differences in system design." *Id.* at 3. Moreover, Alza does not present a single, compelling reason as to why FDA should abandon this precedent and delay the approval of pending ANDA applications so that it may classify different fentanyl transdermal systems as different dosage forms. Finally, the elements that must be included in an ANDA are listed in section 505(j)(2)(A) of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. 355(j)(2)(A): the applicant must show that the active ingredient is the same, that the route of administration and dosage form is the same, that its product is bioequivalent and that certain other requirements are met. Congress was explicit in directing that FDA "may not require that an abbreviated application contain information in addition to that required in [section 505(j)(2)(A)]." *Id.* Consistent with past FDA precedent, the Lavipharm FTS and the Duragesic FTS clearly have the same dosage form, and therefore the FDA may not legally rely on the difference between the Lavipharm FTS and the Duragesic FTS delivery mechanisms as a basis for denying Lavipharm's ANDA.

CONCLUSION

For the foregoing reasons, the above-referenced Citizen Petitions should be denied before January 23, 2005, the date on which the pediatric exclusivity for the Duragesic FTS will expire.

To the extent, however, that FDA is unable to act on the Citizen Petitions before that date, it should, on January 23, 2005, approve any pending ANDAs that are otherwise ready to be approved.

Respectfully submitted,



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